

AMENDMENT

Please amend the application without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows.

In the Specification:

Please replace the title of the application with the following:

-- CONTACTING CELLS WITH MODULATORS OF NOTCH SIGNALLING --

Please replace the figure descriptions on page 12, line 20 – page 13, line 23, with the following:

-- Figure 4 shows a schematic representation of CD4+ T-cells cultured in plates coated with anti-CD3 antibody and Delta-Fc, and resuspended with anti-CD28 antibody, as described in Examples 1 to 3;

Figure 5 shows a schematic representation of a CHO-N2 cell cultured in plates coated with Delta-Fc, and transfected with a Luciferase reporter plasmid, as described in Examples 2 to 8;

Figure 6 shows a schematic representation of a co-culture assay comprising CHO-N2 cells transfected with a Luciferase reporter plasmid and plated, and CHO-Delta or A20-Delta cells, as described in Example 8;

Figure 7 shows ELISA measurements of cytokine production with and without the addition of soluble Fc-delta, as described in Example 3;

Figure 8 shows HES-1 expression relative to 18S rRNA expression with and without Fc-delta, as described in Example 4;

Figure 9 shows ELISA measurements of cytokine production under polarizing conditions, as described in Example 5;

Figure 10 shows cytokine production and compares soluble Fc-delta with plate-bound Fc-delta against control, as described in Example 6;

Figure 11 shows cytokine production and cell proliferation in cells experiencing secondary stimulation, as described in Example 7;

Figures 12A-12D show the results of sample assays using the CHO-Notch2-10xCBF1-Luc reporter cell line with (A) plate-immobilised human Delta-1/Fc fusion protein, (B) plate-immobilised mouse Delta-1/Fc fusion protein, (C) CHO/CHO-human Delta1 co-cultured cells

and (D) A20/A20-mouse Delta1 co-cultured cells as actives against corresponding controls, as described in Example 8;

Figure 13 shows measurements of cytokine production induced by Delta-Fc coated beads in T-cells, as described in Example 10;

Figures 14A and 14B show IL-10 production in the presence of mouse or human Delta1 beads in T-cells from (A) Donor 1 and (B) Donor 2, as described in Example 11;

Figures 15A and 15B show IL-5 production in the presence of mouse or human Delta1 beads in T-cells from (A) Donor 1 and (B) Donor 2, as described in Example 11;

Figure 16 shows IL-10 production in the presence of mouse Delta1 beads, as described in Example 11;

Figure 17 shows IL-5 production in the presence of mouse Delta1 beads, as described in Example 11;

Figure 18 shows cytokine production in the presence of mouse Delta1-Fc beads in T-cells, as described in Example 11;

Figure 19 shows IL-10 production in the presence of Delta1 beads in T-cells at varying bead-to-cell ratios, as described in Example 12;

Figures 20A and 20B show cytokine production in the presence of mouse Delta1-Fc beads in (A) Unseparated CD4⁺ T-cells and (B) Memory CD4⁺CD45RO⁺ T-cells, as described in Example 13;

Figure 21 shows IL-10 production in the presence of Delta-Fc in un-polarised cells, Th1 polarised cells, and Th2 polarised cells, as described in Example 14;

Figures 22A and 22B illustrate (A) a schematic representation of the protocol for activating with Delta alone and (B) a Venn diagram showing numbers of genes with increased expression in response to Delta activation alone, as described in Example 15;

Figure 23 shows a time-course expression profile of Delta-mediated activation of gene expression in Jurkat T-cells, as described in Example 15;

Figures 24A and 24B illustrate (A) a schematic representation of the protocol for activating with both Delta and anti-CD3/CD28 activation, and (B) a Venn diagram showing numbers of genes with increased expression in response to Delta activation in combination with anti-CD3/CD28 activation, as described in Example 15;

Figures 25A and 25B show a time-course expression profile for (A) Delta activation in combination with anti-CD3/CD28 activation and (B) Delta activation alone, as described in Example 15;

Figures 26A-26C show gene expression in response to Delta activation with and without T-Cell Receptor Stimulation for (A) Cip1-interacting zinc finger protein, (B) UMP-CMP kinase, and (C) Helicase, as described in Example 15;

Figure 27 shows the results of transient reporter assays conducted with Jurkat/Notch2 clones with or without immobilised hDLL1-Fc and with or without PMA/ionomycin, as described in Example 16;

Figure 28 shows the reporter assay dose response to the concentration of plate-bound hDLL1-Fc in Jurkat/Notch2 clones, as described in Example 16;

Figure 29 shows a reporter assay dose response to ionomycin concentration, as described in Example 17;

Figure 30 shows the effects of treating Jurkat cells transfected with Human Notch1 intracellular domain and reporter constructs with anti-CD3/CD28 or PMA/ionomycin assessed by fold activation compared to absence of Notch IC (Expt 1) and luminescence (Expt 2), as described in Example 18; --

Please amend the paragraph of page 31, lines 9-20, as follows:

Further homologues of known mammalian Notch ligands may be identified using standard techniques. By a "homologue" it is meant a gene product that exhibits sequence homology, either amino acid or nucleic acid sequence homology, to any one of the known Notch ligands, for example as mentioned above. Typically, a homologue of a known Notch ligand will be at least 20%, preferably at least 30%, identical at the amino acid level to the corresponding known Notch ligand over a sequence of at least 10, preferably at least 20, preferably at least 50, suitably at least 100 amino acids, or over the entire length of the Notch ligand. Techniques and software for calculating sequence homology between two or more amino acid or nucleic acid sequences are well known in the art (see for example <http://www.ncbi.nlm.nih.gov> the website for the National Center for Biotechnology Information and Ausubel et al., Current Protocols in Molecular Biology (1995), John Wiley & Sons, Inc.)